Remarks

This paper amends the specification to add the ABSTRACT OF THE DISCLOSURE and to correct typographical and clerical errors. No new matter is believed to be added in the amendments to the specification. It is requested that the amendments above be entered and that the claims be examined on the merits. Should any questions arise, the Patent and Trademark Office is requested to contact the undersigned attorney.

Respectfully submitted,

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SPECIFICATION REPLACEMENT PARAGRAPHS IN MARKED-UP FORM

On page 4, please delete paragraph **[0007]** and substitute the paragraph below which has been changed with respect to the original paragraph by adding on line 7 of the paragraph after the number 60 the word "degrees".

[0008] Some groups have reported on systemic administration by what has been characterized as "intradermal" injection. In one such report, a comparison study of subcutaneous and what was described as "intradermal" injection was performed (Autret et al, *Therapie 46:*5-8, 1991). The pharmaceutical substance tested was calcitonin, a protein of a molecular weight of about 3600. Although it was stated that the drug was injected intradermally, the injections used a 4 mm needle pushed up to the base at an angle of 60 **degrees**. This would have resulted in placement of the injectate at a depth of about 3.5 mm and into the lower portion of the reticular dermis or into the subcutaneous tissue rather than into the vascularized papillary dermis. If, in fact, this group injected into the lower portion of the reticular dermis rather than into the subcutaneous tissue, it would be expected that the substance would either be slowly absorbed in the relatively less vascular reticular dermis or diffuse into the subcutaneous region to result in what would be functionally the same as subcutaneous administration and absorption. Such actual or functional subcutaneous administration would explain the reported lack of difference between subcutaneous and what was characterized as intradermal administration, in the times at which maximum plasma concentration was reached, the concentrations at each assay time and the areas under the curves.

On pages 5 and 6, please delete paragraph **[0011]** and substitute the paragraph below which has been changed with respect to the original paragraph by substituting on line 15 of the paragraph, the words "significant beneficial" for "signifigant benefical".

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[00012] The present disclosure relates to a new parenteral administration method based on directly targeting the dermal space whereby such method dramatically alters the pharmacokinetics (PK) and pharmacodynamics (PD) parameters of administered substances. By the use of direct intradermal (ID) administration means hereafter referred to as dermal-access means, for example, using microneedle-based injection and infusion systems (or other means to accurately target the intradermal space), the pharmacokinetics of many substances including drugs and diagnostic substances, which are especially protein and peptide hormones, can be altered when compared to traditional parental administration routes of subcutaneous and intravenous delivery. These findings are pertinent not only to microdevice-based injection means, but other delivery methods such as needleless or needle-free ballistic injection of fluids or powders into the ID space, Mantoux-type ID injection, enhanced iontophoresis through microdevices, and direct deposition of fluid, solids, or other dosing forms into the skin. Disclosed is a method to increase the rate of uptake for parenterally-administered drugs without necessitating IV access. One **[signifigant beneficial]** **significant beneficial** effect of this delivery method is providing a shorter T_{max}.(time to achieve maximum blood concentration of the drug). Potential corollary benefits include higher maximum concentrations for a given unit dose (C_{max}), higher bioavailability, more rapid uptake rates, more rapid onset of pharmacodynamics or biological effects, and reduced drug depot effects. According to the present invention, improved pharmacokinetics means increased bioavailability, decreased lag time (T_{lag}), decreased T_{max}, more rapid absorption rates, more rapid onset and/or increased C_{max} for a given amount of compound administered, compared to subcutaneous, intramuscular or other non-IV parenteral means of drug delivery.

On page 8, delete paragraph **[0015]** and substitute the paragraph below which has been changed by substituting on line 21 of the paragraph, the word "sequestered" for "sequested".

[00016] As used herein, intradermal is intended to mean administration of a substance into the dermis in such a manner that the substance readily reaches the

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richly vascularized papillary dermis and is rapidly absorbed into the blood capillaries and/or lymphatic vessels to become systemically bioavailable. Such can result from placement of the substance in the upper region of the dermis, i.e. the papillary dermis or in the upper portion of the relatively less vascular reticular dermis such that the substance readily diffuses into the papillary dermis. It is believed that placement of a substance predominately at a depth of at least about 0.3 mm, more preferably, at least about 0.4 mm and most preferably at least about 0.5 mm up to a depth of no more than about 2.5 mm, more preferably, no more than about 2.0 mm and most preferably no more than about 1.7 mm will result in rapid absorption of macromolecular and/or hydrophobic substances. Placement of the substance predominately at greater depths and/or into the lower portion of the reticular dermis is believed to result in the substance being slowly absorbed in the less vascular reticular dermis or in the subcutaneous region either of which would result in reduced absorption of macromolecular and/or hydrophobic substances. The controlled delivery of a substance in this dermal space below the papillary dermis in the reticular dermis, but sufficiently above the interface between the dermis and the subcutaneous tissue, should enable an efficient (outward) migration of the substance to the (undisturbed) vascular and lymphatic microcapillary bed (in the papillary dermis), where it can be absorbed into systemic circulation via these microcapillaries without being **[sequested]** **<u>sequestered</u>** in transit by any other cutaneous tissue compartment.

On page 10, please delete paragraph **[0020]** and substitute the paragraph below which has been changed by substituting on line 6 of the paragraph, the words "agent concentrations" for "agentconcentrations".

[00021] Another benefit of the invention is no change in pharmacodynamic mechanism or biological response mechanism. As stated above, administered drugs by the methods taught by the applicants still exert their effects by the same biological pathways that are intrinsic to other delivery means. Any pharmacodynamic changes are related only to the difference patterns of appearance, disappearance, and drug or

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diagnostic **[agentconcentrations]** **agent concentrations** present in the biological system.

On pages 10 and 11, please delete paragraph **[0022]** and substitute the paragraph below which has been changed by substituting at line 16 of the paragraph, the word "entrapment" for "entrappment".

[00023] Another benefit of the invention is removal of the physical or kinetic barriers invoked when drugs passes through and becomes trapped in cutaneous tissue compartments prior to systemic absorption. Elimination of such barriers leads to an extremely broad applicability to various drug classes. Many drugs administered subcutaneously exert this depot effect -- that is, the drug is slowly released from the SC space, in which it is trapped, as the rate determining step prior to systemic absorption, due to affinity for or slow diffusion through the fatty adipose tissue. This depot effect results in a lower C_{max} and longer T_{max}, compared to ID, and can result in high inter-individual variability of absorption. This effect is also pertinent for comparison to transdermal delivery methods including passive patch technology, with or without permeation enhancers, iontophoretic technology, sonopheresis, or stratum corneum ablation or disruptive methods. Transdermal patch technology relies on drug partitioning through the highly impermeable stratum corneum and epidermal barriers. Few drugs except highly lipophilic compounds can breach this barrier, and those that do, often exhibit extended offset kinetics due to tissue saturation and **[entrappment]** **entrapment** of the drugs. Active transdermal means, while often faster than passive transfer means, are still restricted to compound classes that can be moved by charge repulsion or other electronic or electrostatic means, or carried passively through the transient pores caused by cavitation of the tissue during application of sound waves. The stratum corneum and epidermis still provide effective means for inhibiting this transport. Stratum corneum removal by thermal or laser ablation, abrasive means or otherwise, still lacks a driving force to facilitate penetration or uptake of drugs. Direct ID administration by mechanical means overcomes the kinetic barrier properties of skin, and is not limited by the

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pharmaceutical or physicochemical properties of the drug or its formulation excipients.

On page 12, please delete paragraph **[0024]** and substitute the paragraph below which has been changed by substituting on line 2 of the paragraph, the word "agents" for "aegents".

[0025] Another benefit of the invention is reduced degradation of drugs and diagnostic **[agaents]** **agents** and/or undesirable immunogenic activity. Transdermal methods using chemical enhancers or iontophoresis, or sonophoresis or electroporation or thermal poration require that a drug pass through the viable epidermal layer, which has high metabolic and immunogenic activity. Metabolic conversion of substances in the epidermis or sequestration by immunoglobulins reduces the amount of drug available for absorption. The ID administration circumvents this problem by placing the drug directly in the dermis, thus bypassing the epidermis entirely.

On pages 12 and 13, please delete paragraph **[0026]** and substitute the paragraph below which has been changed by substituting on line 10 of the paragraph, the word "pharmacokinetics" for "pharmacokenetics".

[0027] These and other benefits of the invention are achieved by directly targeting absorption by the papillary dermis and by controlled delivery of drugs, diagnostic agents, and other substances to the dermal space of skin. The inventors have found that by specifically targeting the intradermal space and controlling the rate and pattern of delivery, the pharmacokinetics exhibited by specific drugs can be unexpectedly improved, and can in many situations be varied with resulting clinical advantage. Such **[pharmacokenetics]** **pharmacokinetics** cannot be as readily obtained or controlled by other parenteral administration routes, except by IV access.

On pages 17 and 18, please delete paragraph **[0043]** and substitute the paragraph below which has been changed by substituting on line 19 of the paragraph, the word "subcutaneous" for "subcutanous".

[0043] By "improved pharmacokinetics" it is meant that an enhancement of pharmacokinetic profile is achieved as measured, for example, by standard pharmacokinetic parameters such as time to maximal plasma concentration (T_{max}), the magnitude of maximal plasma concentration (C_{max}) or the time to elicit a minimally detectable blood or plasma concentration (T_{lag}). By enhanced absorption profile, it is meant that absorption is improved or greater as measured by such pharmacokinetic parameters. The measurement of pharmacokinetic parameters and determination of minimally effective concentrations are routinely performed in the art. Values obtained are deemed to be enhanced by comparison with a standard route of administration such as, for example, subcutaneous administration or intramuscular administration. In such comparisons, it is preferable, although not necessarily essential, that administration into the intradermal layer and administration into the reference site such as subcutaneous administration involve the same dose levels, i.e. the same amount and concentration of drug as well as the same carrier vehicle and the same rate of administration in terms of amount and volume per unit time. Thus, for example, administration of a given pharmaceutical substance into the dermis at a concentration such as 100 μg/ml and rate of 100 μL per minute over a period of 5 minutes would, preferably, be compared to administration of the same pharmaceutical substance into the **[subcutanous]** **subcutaneous** space at the same concentration of 100 μg/ml and rate of 100 μL per minute over a period of 5 minutes.

On page 18, please delete the paragraph **[0044]** and substitute the paragraph below which has been changed by substituting on line 7 of the paragraph, the word "hydrophilic" for "hydrophillic".

[0045] The enhanced absorption profile is believed to be particularly evident for substances which are not well absorbed when injected subcutaneously such as, for example, macromolecules and/or hydrophobic substances. Macromolecules are, in general, not well absorbed subcutaneously and this may be due, not only to their size relative to the capillary pore size, it may also be due to their slow diffusion through the interstitium because of their size. It is understood that macromolecules can possess discrete domains having a hydrophobic and/or **[hydrophillic]** **hydrophilic** nature. In contrast, small molecules which are hydrophilic are generally well absorbed when administered subcutaneously and it is possible that no enhanced absorption profile would be seen upon injection into the dermis compared to absorption following subcutaneous administration. Reference to hydrophobic substances herein is intended to mean low molecular weight substances, for example substances with molecular weights less than 1000 Daltons, which have a water solubility which is low to substantially insoluble

On page 20, please delete paragraph **[0048]** and substitute the paragraph below which has been changed by substituting on line 2 of the paragraph the words "bolus and" for "bolusand" and by substituting on line 21 of the paragraph the word "electromagnetic" for "electrmagnetic."

[0049] The administration methods useful for carrying out the invention include both **[bolusand]** **bolus and** infusion delivery of drugs and other substances to humans or animals subjects. A bolus dose is a single dose delivered in a single volume unit over a relatively brief period of time, typically less than about 10 minutes. Infusion administration comprises administering a fluid at a selected rate that may be constant or variable, over a relatively more extended time period, typically greater than about 10 minutes. To deliver a substance the dermal-access means is placed adjacent to the skin of a subject providing directly targeted access within the intradermal space and the substance or substances are delivered or administered into the intradermal space where they can act locally or be absorbed by the bloodstream and be distributed systematically. The dermal-

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access means may be connected to a reservoir containing the substance or substances to be delivered. The form of the substance or substances to be delivered or administered include solutions thereof in pharmaceutically acceptable diluents or solvents, emulsions, suspensions, gels, particulates such as micro- and nanoparticles either suspended or dispersed, as well as in-situ forming vehicles of the same. Delivery from the reservoir into the intradermal space may occur either passively, without application of the external pressure or other driving means to the substance or substances to be delivered, and/or actively, with the application of pressure or other driving means. Examples of preferred pressure generating means include pumps, syringes, elastomer membranes, gas pressure, piezoelectric, electromotive, **[electromagnetic]** **electromagnetic** pumping, or Belleville springs or washers or combinations thereof. If desired, the rate of delivery of the substance may be variably controlled by the pressure-generating means. As a result, the substance enters the intradermal space and is absorbed in an amount and at a rate sufficient to produce a clinically efficacious result.

On page 22, please delete paragraph **[0051]** and substitute the paragraph below which has been changed by substituting on page 22, line 11, the word "synthetic" for the word "syntheic".

[0052] Therapeutic substances which can be used with the present invention include Alpha-1 anti-trypsin, Anti-Angiogenesis agents, Antisense, butorphanol, Calcitonin and analogs, Ceredase, COX-II inhibitors, dermatological agents, dihydroergotamine, Dopamine agonists and antagonists, Enkephalins and other opioid peptides, Epidermal growth factors, Erythropoietin and analogs, Follicle stimulating hormone, G-CSF, Glucagon, GM-CSF, granisetron, Growth hormone and analogs (including growth hormone releasing hormone), Growth hormone antagonists, Hirudin and Hirudin analogs such as Hirulog, IgE suppressors, Insulin, insulinotropin and analogs, Insulin-like growth factors, Interferons, Interleukins, Luteinizing hormone, Luteinizing hormone releasing hormone and analogs, Heparins, Low molecular weight heparins and other natural, modified, or

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[syntheic] **synthetic** glycoaminoglycans, M-CSF, metoclopramide, Midazolam, Monoclonal antibodies, Peglyated antibodies, Pegylated proteins or any proteins modified with hydrophilic or hydrophobic polymers or additional functional groups, Fusion proteins, Single chain antibody fragments or the same with any combination of attached proteins, macromolecules, or additional functional groups thereof, Narcotic analgesics, nicotine, Non-steroid anti-inflammatory agents, Oligosaccharides, ondansetron, Parathyroid hormone and analogs, Parathyroid hormone antagonists, Prostaglandin antagonists, Prostaglandins, Recombinant soluble receptors, scopolamine, Serotonin agonists and antagonists, Sildenafil, Terbutaline, Thrombolytics, Tissue plasminogen activators, TNF - , and TNF - antagonist, the vaccines, with or without carriers/adjuvants, including prophylactics and therapeutic antigens (including but not limited to subunit protein, peptide and polysaccharide, polysaccharide conjugates, toxoids, genetic based vaccines, live attenuated, reassortant, inactivated, whole cells, viral and bacterial vectors) in connection with, addiction, arthritis, cholera, cocaine addiction, diphtheria, tetanus, HIB, Lyme disease, meningococcus, measles, mumps, rubella, varicella, yellow fever, Respiratory syncytial virus, tick borne Japanese encephalitis, pneumococcus, streptococcus, typhoid, influenza, hepatitis, including hepatitis A, B, C and E, otitis media, rabies, polio, HIV, parainfluenza, rotavirus, Epstein Barr Virus, CMV, chlamydia, non-typeable haemophilus, moraxella catarrhalis, human papilloma virus, tuberculosis including BCG, gonorrhoea, asthma, atheroschlerosis malaria, E-coli, Alzheimer's Disease, H. Pylori, salmonella, diabetes, cancer, herpes simplex, human papilloma and the like other substances including all of the major therapeutics such as agents for the common cold, Anti-addiction, anti-allergy, anti-emetics, anti-obesity, antiosteoporeteic, anti-infectives, analgesics, anesthetics, anorexics, antiarthritics, antiasthmatic agents, anticonvulsants, anti-depressants, antidiabetic agents, antihistamines, anti-inflammatory agents, antimigraine preparations, antimotion sickness preparations, antinauseants, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, anticholinergics, benzodiazepine antagonists, vasodilators, including general, coronary, peripheral and cerebral,

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bone stimulating agents, central nervous system stimulants, hormones, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetrics, prostaglandins, proteins, peptides, polypeptides and other macromolecules, psychostimulants, sedatives, and sexual hypofunction and tranquilizers.

On page 31, please delete paragraph **[0073]** and substitute the paragraph below which has been changed by deleting on line 18 of the paragraph, the words "NEED CLAIM."

[0074] Bolus delivery of Lantus long-acting insulin was delivered via the ID route . Lantus is an insulin solution that forms microprecipitates at the administration site upon injection. These microparticulates undergo slow dissolution within the body to provide (according to the manufacturer's literature) a more stable low level of circulating insulin than other current long-acting insulin such as crystalline zinc precipitates (e.g. Lente, NPH). Lantus insulin (10 U dose, 100 uL) was administered to diabetic Yucatan Mini pigs using the dermal access design SS3_34 and by the standard SC method as previously described. Referring to Figure 5, when administered via the ID route, similar PK profiles were obtained relative to SC. Minor distinctions include a slightly higher "burst" immediately after the ID insulin delivery. This demonstrates that the uptake of even very high molecular weight compounds or small particles is achievable via ID administration. More importantly this supports the fact that the biological clearance mechanism in the body is not appreciably changed by the administration route, nor is the way in which that the drug substance is utilized. This is extremely important for drugs compounds that have a long circulating half-life (examples would be large soluble receptor compounds or other antibodies for cancer treatment, or chemically modified species such as PEGylated drugs). **[NEED CLAIM]**

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